REMARKS

Status Summary

Claims 1, 5-13, 16-17, and 19-27 are pending. Claims 1, 5-13, 16-17, and 19-27 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over previously cited references, as explained herein below. Claims 1, 5-13, 16-17, and 19-27 are also provisionally rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claims in the co-pending parent application U.S. Appl. No. 09/435,992. Reconsideration in view of the following remarks is respectfully requested.

Rejection of Claims Under 35 U.S.C. § 103(a)

Claims 1, 5-13, 16-17, and 19-27 are pending. Claims 1, 5-13, 16-17, and 19-27 are rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over U.S. Patent No. 6,287,537 to Kaminski et al. (Kaminski) and/or U.S. Patent No. 5,843,439 to Anderson et al. (Anderson) in view of Gruss et al. (1997) *Leukemia & Lymphoma* 24:393-422 (Gruss), Carbone et al. (1995), *Am J Pathol* 147:912-922 (Carbone), and U.S. Patent No. 6,001,358 to Black et al. (Black). The examiner further relies on pages 41-45 of the specification for the teaching that chemotherapeutic treatments, including combination therapy of malignancies, were known and practiced at the time of the invention. This rejection is respectfully traversed.

The examiner bears the burden of presenting a *prima facie* case for obviousness, which requires: (1) some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) the teaching or suggestion of all the claim limitations of the applicant's invention in the combined prior art references; and (3) a reasonable expectation of success. MPEP § 2143. Applicants respond that the examiner has failed to meet this burden. Applicants further respond that the unexpected results of the present inventive method support the non-obviousness of the now claimed combination therapy.

I. The Cited References Lack a Specific Suggestion or Motivation To Perform the Claimed Combination

With regard to the first of these factors, suggestion or motivation to combine, such motivation may be found "where there is some teaching, suggestion, or motivation ... either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art." MPEP § 2143.01 (citing *In re Kotzab*, 217 F.3d 1365, 1370

55 USPQ2d 1313, 1317 (Fed. Cir. 2000)). Not only must such motivation be present, "there must be some teaching, suggestion or motivation in the prior art to make the specific combination that was made by the applicant." *In re Dance,* 160 F.3d 1339, 1343, 48 USPQ2d 1635, 1637 (Fed. Cir. 1998) (emphasis added) (citing *In re Raynes,* 7 F.3d 1037, 1039, 28 USPQ2d 1630, 1631 (Fed. Cir. 1993); *In re Oetiker,* 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992).

The fact that the prior art teaches individual elements of the claimed invention that are generally known or within the capabilities of one with knowledge in the art is not, however, sufficient to establish a *prima facie* case of obviousness without any specific teaching or suggestion for making the combination. Accordingly, in a proper analysis of obviousness, the level of knowledge of one with ordinary skill in the art cannot be substituted for a clear suggestion to make a combination. *See A-Site Corp. v. VSI International Inc.,* 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999).

Therefore, the examiner is required to show how and why the applicant would have been motivated to combine the references in the manner combined by the examiner. The examiner has not done so, but has simply described the utility of individual CD40L and CD20 therapies to support his argument that a skilled artisan would have been motivated to perform the presently claimed combination therapy.

The examiner's suggestion that anti-CD20 therapy be combined with administration of anti-CD40L antibodies for the treatment of non-Hodgkin's lymphoma is at best a proposal to try the combination, which is an improper standard for determining obviousness. The Federal Circuit has consistently held that "obvious to try" is not to be equated with obviousness under 35 U.S.C. § 103. *See e.g., In re O'Farrell,* 853 F.2d 894, 903, 7 U.S.P.Q.2d 1673, 1680 (Fed. Cir. 1988). The end result of a pursuit is not obvious simply because it may be obvious to try to achieve such a result. In the instant case, the resulting improved therapeutic method, which is a combination of existing methods, which combination yields unexpected efficacy for treating non-Hodgkin's lymphoma, is not obvious simply because it may have been obvious to try any combination of existing methods.

The examiner relies on Kaminski and Anderson as allegedly supporting that "the prior art taught combination therapy to various B cell malignancies, including B cell non-Hodgkin's lymphoma with CD20-specific antibodies at the time the invention was made." The examiner further states that "[p]roviding radiotherapy and chemotherapy was known and

routinely practiced at the time the invention was made in the treatment of non-Hodgkin's lymphomas at the time the invention was made." Official Action, at page 3, ¶ 3.

Applicants respond that the examiner's arguments identify a combination therapy, *i.e.* radiotherapy in combination with chemotherapy, which combination is not presently claimed. The cited references lack any specific suggestion or motivation to combine anti-CD20 therapy with anti-CD40L treatment, as described below, and are thereby insufficient to support a finding of obviousness.

Kaminski makes only a general statement that anti-CD20 (B1) antibodies can be used in combination with *any* other antibody. Kaminski summarizes this aspect of the invention as follows: "A third method using B1 antibody comprises administering to a patient a large amount of an unlabeled antibody, which can be B1 but can also be other antibodies, prior to administration of a therapeutic dose of labeled B1 antibody." Summary of the invention, at column 5, lines 51-54. The '537 patent, however, does not include the term "CD40L" or any reference to CD40/CD40L signaling. As such, Kaminski fails to specifically suggest or motivate combination of anti-CD20 therapy, as described by Kaminski, with anti-CD40L therapy as now claimed.

Anderson describes combination therapies that include a cold anti-CD20 antibody and a radiolabeled anti-CD20 antibody, optionally further in combination with chemotherapy. Anderson also fails to specifically suggest or motivate combination of anti-CD20 therapy with anti-CD40L therapy as now claimed. Similar to Kaminski, the '439 patent to Anderson does not include the term "CD40L" or any reference to CD40/CD40L signaling.

A general suggestion to concurrently employ two or more cancer treatments, in the absence of a suggestion or motivation to perform the specific elements of the claimed invention, stands as a mere suggestion to try. Both Kaminski and Anderson, or a combination thereof, fail to suggest or motivate the specific combination of an anti-CD40L antibody in combination with an anti-CD20 antibody.

The examiner further relies on pages 41-45 of the instant specification to support that combination therapies for the treatment of lymphomas were known and practiced at the time the invention was made. Official Action, page 2, ¶ 5 (item 4). Applicants respond that the referenced pages of the application refer to methods for antibody formulation and administration, as known in the art, but does not include any concession that a therapy

comprising anti-CD20 antibodies in combination with anti-CD40L antibodies was known, suggested, or motivated by the art at the time of the invention.

Gruss, Carbone, and Black do not cure the deficiencies of Kaminski and/or Anderson as they similarly fail to specifically suggest or motivate the invention now claimed. In particular, the teachings of Gruss, Carbone, and Black describe the role of CD40/CD40L signaling in lymphoma progression and management, but lack any reference to treatment methods that include anti-CD20 therapy.

Carbone teaches expression of CD40 and CD40L on B cells and T cells, respectively, of a non-Hodgkin's lymphoma patient. Carbone proposes a mechanism for lymphoma progression, which relevance merits further study. Carbone states "[t]he functional significance of the expression of CD40L on reactive T lymphocytes of B-cell NHL also deserves *speculation* . . . . provided [is] morphological evidence that the CD40/CD40L pathway *may* play an important role in cell contact-dependent interaction of tumor B cells . . . . (page 920, emphasis added). Thus, Carbone does not teach a method for cancer therapy, and in particular lacks suggestion or motivation of method that includes CD40L blockade in combination with anti-CD20.

Gruss teaches that CD40/CD40L signaling enhances B cell activation and growth. Gruss also acknowledges suggestions that that recombinant soluble CD40L, which has anti-proliferative and pro-apoptotic effects, can be used for the treatment of lymphoma, including high grade lymphoma. To clarify, the text cited by the examiner states that recombinant CD40L activities "*may* offer" an attractive therapeutic strategy (page 405, col. 1, ¶ 1, emphasis added). Similarly, Gruss admonishes that the "functional activity of [CD40] in [B cell malignancies] and its significance for tumor cell proliferation remains to be elucidated (page 404, column 2, ¶ 2). Further, Gruss does not suggest or motivate a therapy comprising soluble CD40L treatment in combination with anti-CD20 treatment.

Black describes preparation of humanized anti-CD40L antibodies and suggests their utility for cancer therapy. However, Black does not teach therapeutic methods using the disclosed anti-CD40L antibodies in combination with anti-CD20 antibodies.

Based on Carbone, Gruss, and Black, the examiner contends that "[i]t would have been expected that targeting CD40L on high grade B-NHLs would have left such cells more sensitive to treatment with anti-CD20 antibodies." Official Action, page 4, ¶ 2. This contention appears to represent the examiner's opinion only, or the examiner's inference

following a review of the instant application, as the examiner has not pointed to any evidence in the cited art to substantiate this statement.

The examiner further states that "[g]iven the expression of CD20 and CD40 and the ability of activation via CD20 and/or CD40, the ordinary artisan would have been motivated to target B cell non-Hodgkin's lymphoma directly with radiolabeled CD20-specific antibodies and to diminish activation of said B cell leukemia by blocking activation by CD40 ligand expressing T cell with CD40L-specific antibodies." Official Action, page 4, ¶ 4. Applicants similarly respond that the examiner has proposed the combination now claimed without specific reference to any suggestion or motivation for the proposed combination in the cited art.

Based on the foregoing arguments, applicants believe that a *primae facie* case of non-obviousness has not been made, and thus the rejection of claims under 35 U.S.C. § 103(a) should be withdrawn.

II. The Claimed Methods Produce Unexpected Results

Applicants further respond that the present invention produces synergistic effects not predicted by the sum of the individual therapies. The Court of Appeals for the Federal Circuit has repeatedly held that secondary considerations such as unexpected results can effectively rebut a finding of *primae facie* obviousness. *See e.g., In re Geisler*, 116 F.3d 1465, 1469, 43 U.S.P.Q.2d 1362 (Fed. Cir. 1997) (quoting *In re Soni*, 54 F.3d 746, 750, 34 U.S.P.Q.2d 1684, 1687 (Fed. Cir. 1995). Thus, even assuming *arguendo* that a *primae facie* case of obviousness has been established, the unexpected and synergistic qualities of the presently claimed combination are sufficient to overcome the examiner's finding.

The examiner dismisses the observed synergy between anti-CD40L antibodies and anti-CD20 antibodies, as disclosed in the instant specification, stating that the disclosed unexpected results "do not appear to be inconsistent with the expected roles of blocking CD40 interaction with CD40L and targeting CD20 in the treatment of B cell malignancy, including B cell non-Hodgkin's lymphoma, taught by the combination of references in the prior art." Official Action, page 3, ¶ 3.

Applicants respond that a rejection of claims based on obviousness is effectively overcome by showing that the claimed invention exhibits unexpected superior efficacy. Contrary to the assertion of the examiner, the disclosed synergistic effects are inconsistent with a sum of the therapeutic efficacies of anti-CD20 and anti-CD40L antibodies when

administered individually. A more durable and potent clinical response, as now observed when anti-CD20 and anti-CD40L therapies are combined, was unpredicted prior to disclosure of the instant application. The unexpectedness of the inventive methods are sufficient to rebut a rejection of claims based on a prior suggestion or motivation to perform the methods, notwithstanding applicants arguments that such combination is not suggested or motivated by the prior art, herein above.

Based on the foregoing arguments, applicant believes that claims 1, 5-13, 16-17 and 19-27 comply with the requirements of 35 U.S.C. § 103(a). Thus, applicant respectfully requests that the rejection of claims 1, 5-13, 16-17 and 19-27 under § 103(a) be withdrawn.

Rejection of Claims Based on Non-Statutory
Obviousness-Type Double Patenting

Claims 1, 5-13, 16-17, and 19-27 are also provisionally rejected based on non-statutory obviousness-type double patenting as allegedly unpatentable over claims in the copending parent application U.S. Appl. No. 09/435,992. Applicants respond that a terminal disclaimer will be filed when one or more pending claims is in condition for allowance.

Conclusion

All rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

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